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New chemotherapy options for the treatment of malignant gliomas

[Brain And Nervous System]

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Outline

Abstract

Chemotherapy remains part of the treatment triad that includes surgery and radiation therapy for the management of malignant gliomas. In recent years there has been an increased understanding of the molecular pathways of malignant transformation. Based on this research, new drugs have been evaluated, with specific cellular targets in mind that can be modified or inhibited. Many of these agents are now being tested in phase I and II clinical trials and have shown some promising results. Clearly, not all patients with malignant gliomas respond equally to chemotherapy. Recent evidence suggests that certain molecular markers may predict chemosensitivity in some tumor types, particularly anaplastic oligodendroglioma. This article reviews recent trends in the use of chemotherapy and clinical trials of new therapies for adults with malignant gliomas.

Abbreviations **BCNU** 1,3-bis(2-chloroethyl)-1-nitrosourea, **MMP** matrix metalloproteinases, **PCV** procarbazine, CCNU, vincristine combination, **PDGF** platelet-derived growth factor,

Standard methods for the treatment of patients with malignant gliomas, including glioblastoma multiforme, anaplastic astrocytoma, anaplastic oligodendroglioma, and oligoastrocytoma, are surgery, irradiation, and chemotherapy. Surgery is needed to establish a pathologic diagnosis, and extensive tumor resection improves survival compared with limited resections or biopsy only. Postsurgical irradiation has also been demonstrated in clinical trials to improve survival outcome. The benefit of chemotherapy is less clear.

Current recommendations for the treatment of patients with newly diagnosed malignant glioma with chemotherapy is based on early studies that did not take into account factors that have since been found to influence outcome. These include age, Karnofsky performance status, and tumor histology. Younger patients undergoing surgical resection who have a high Karnofsky performance status with tumors other than glioblastoma multiforme do significantly better than older patients with glioblastoma multiforme diagnosed by biopsy alone. Furthermore, many of these earlier studies lacked the statistical power to reliably detect outcome differences within these patient subsets.

A recent meta-analysis that included 16 studies published between 1975 and 1989 and involved more than 3000 patients concluded that a proportionate increase occurred in survival rates of patients treated with radiation and chemotherapy compared with those treated with radiation alone [1]; however, when the results were analyzed with respect to histology, only a subpopulation of patients with either anaplastic astrocytoma or glioblastoma multiforme had any benefit with chemotherapy. These were patients with a good performance status, minimal residual disease, and younger age. So the question of whether postradiation chemotherapy benefits the majority of patients with malignant gliomas remains. The Northern California Oncology Group conducted a phase III trial that compared postradiotherapy chemotherapy using either single-agent BCNU (1,3-bis[2-chloroethyl]-1-nitrosourea) or the drug combination of procarbazine, lomustine, and vincristine (PCV) for patients with anaplastic astrocytoma and glioblastoma multiforme [2]. They found that patients with anaplastic astrocytoma treated with PCV chemotherapy after radiation had a median survival of 157 weeks compared with 82 weeks if BCNU was used. No statistical difference was found in survival with the two chemotherapy regimens in the glioblastoma multiforme group. Based on this study, one of the current recommendations for patients with anaplastic astrocytoma is to be treated with PCV chemotherapy after radiation; however, a more recent retrospective analysis of data compiled by the Radiation Therapy Oncology Group was performed to determine whether any differences could be found in outcome for anaplastic astrocytoma patients treated with BCNU versus PCV. This study showed no survival advantage for the three-drug regimen, suggesting that either might be appropriate options for treatment [3].

The treatment of patients with recurrent malignant gliomas with chemotherapy also needs to be defined further. The same prognostic factors that portend a good response in newly diagnosed tumors is thought to be important in recurrent disease. Interpretation of previous data is confounded by these factors and by the limited and sometimes inconsistent definition of response criteria. The most common chemotherapy agents used in the recurrent setting are the nitrosoureas, either single-agent BCNU or the combination of PCV. The next line of single-agent therapy is often a platinum-based agent, such as carboplatin or cisplatin. Other commonly used drugs include high-dose tamoxifen, procarbazine, and combinations of the above agents. Unfortunately, the reported response rates for chemotherapy used in the treatment of patients with recurrent disease is low and varies between 10% and 40%, with progression-free survival of only several months.

New agents are being developed to treat patients with malignant gliomas. A further

understanding of the molecular biology of these tumors has opened the door for different avenues of chemotherapy attack. Increasingly, inhibitors of signal transduction and angiogenesis, as well as anti-invasion agents, are being evaluated for use in the treatment of these patients. We also now recognize that not all patients with gliomas respond equally to chemotherapy. Some patients with anaplastic oligodendroglioma have shown exceptional chemosensitivity. Evidence suggests that molecular markers may help in predicting chemosensitivity in these patients. This review discusses new chemotherapy options for adults with malignant gliomas and briefly discusses clinical trials currently being conducted around the United States.

Cytotoxic chemotherapy

Two new drugs, temozolomide and irinotecan, have shown promise in the treatment of patients with malignant gliomas. Temozolomide is an imidazotetrazine derivative developed as an alternative to dacarbazine. It is an oral agent that exerts its antitumor effect by methylation of DNA. Temozolomide has been tested in the setting of newly diagnosed and recurrent gliomas and was found to have good response results [4,5,6••]. Results of a phase II study in recurrent anaplastic gliomas showed a combined response and stabilization rate of 60%, with a progression-free survival rate of 48% at 6 months [7]. It is currently undergoing phase II and III testing in the adjuvant and neoadjuvant settings. Studies are also being conducted using this drug in combination with standard chemotherapy agents, such as BCNU. Temozolomide is currently under review by the US Food and Drug Administration (FDA) for use as a standard agent in the treatment of patients with recurrent anaplastic astrocytomas.

Irinotecan, or CPT-11, is an analog of camptothecin. CPT-11 is an intravenous drug that has been approved for use in the treatment of patients with colon cancer. Its mechanism of action is inhibition of topoisomerase I. This enzyme plays a critical role in DNA replication and transcription. The enzyme functions normally during DNA replication to cause transient breaks in a single strand of DNA, releasing the torsional strain caused by synthesis of a new strand of DNA or RNA around a double helix. CPT-11 targets this topo I–DNA complex, stabilizing it and inhibiting the reannealing of the parent DNA. When an advancing replication fork collides with the CPT-11 topo I–DNA complex, double-stranded DNA breaks occur that lead to cell death. Early trials being conducted on malignant gliomas have demonstrated a good response with CPT-11 when used as a single agent [8]. In one study, 60 patients with recurrent malignant gliomas were treated using a dose of 125 mg/m^2 weekly for 4 weeks, followed by a 2-week rest. Partial responses were seen in 10 of 49 evaluable patients with glioblastoma multiforme and 1 of 8 evaluable patients with anaplastic astrocytoma. Toxicity was minimal, suggesting that more formal phase I studies are needed in this patient population. New phase I and II trials are being conducted, together with studies using CPT-11 in combination with standard drugs for recurrent gliomas.

Signal transduction inhibitors

Multiple genetic events contribute to the malignant transformation of gliomas. In some cases, tumor cells have amplification of genes encoding for proteins that stimulate cell growth. Several of these proteins are known to be overexpressed in a portion of malignant gliomas. This is particularly true for the family of protein-tyrosine kinase receptors, such as the platelet-derived growth factor (PDGF) receptor. Several reports note the coexpression of PDGF and its receptors by tumor cells or cells supporting tumor growth, suggesting both autocrine and paracrine mechanisms for PDGF-mediated tumor growth. The PDGF stimulates kinase activity in a variety

of cell types through binding to the PDGF tyrosine kinase receptor [9•,10].

Leflunomide, or SU-101, is a small synthetic molecule that inhibits the PDGF receptor–signaling pathway. It has been tested in a phase I trial, with objective responses noted in some patients [11]. In that study, 42 patients with recurrent malignant gliomas were treated using a 24-hour continuous infusion weekly for 4 weeks. Four patients had an objective regression of tumor, and 7 other patients had stabilization of disease in this phase I study. Phase II results have also been encouraging, prompting a multicenter phase III clinical trial that has since been initiated to establish efficacy in patients with recurrent glioblastoma multiforme. This study randomizes patients to treatment with either SU-101 or single-agent procarbazine chemotherapy. In addition, a phase II trial combining SU-101 with BCNU in patients with glioblastoma multiforme has opened.

The agent SU-101 is one of several new agents that target proteins or receptors involved with signal transduction. Others include bryostatin, UCN-01, several farnesyl transferase inhibitors, hypericen, suramin, and SU-5271 [12•]. Tamoxifen, when given in very high doses, is known to be a nonselective inhibitor of protein kinase C and has demonstrated efficacy for patients with recurrent malignant gliomas. The other agents mentioned earlier, such as SU-101, remain in the clinical trial phase.

Matrix metalloproteinase inhibitors

Matrix metalloproteinases (MMPs) are a family of enzymes responsible for normal turnover and remodeling of the extracellular matrix. MMPs are required for tumor angiogenesis and invasion. Elevated levels of MMPs are seen during tumor growth, and this observation has led to the development of MMP inhibitors as one strategy to treat patients with cancer [13,14]. Marimistat (British Biotech, Annapolis, MD) is one drug in this class of MMP inhibitors. Phase I and II testing has been completed in several tumor types using this drug, with encouraging results. It has now been evaluated in a randomized, placebo-controlled phase III trial for patients with newly diagnosed glioblastoma multiformes. The study randomized patients to receive Marimastat or placebo following standard external irradiation. The study design was based on the hope that MMP inhibitors would be more likely to confer a survival benefit when used early in the disease process, ideally during a period of disease stabilization. Inhibition of MMP could potentially defer the development of progression in these patients. Results from this trial are expected soon. Other anti-invasion agents being studied are Bay 12-9566 and Ag334.

Angiogenesis inhibitors

Several drugs are being studied because of their ability to inhibit angiogenesis. Thalidomide is one such agent and was developed in the early 1960s as a sedative. It was withdrawn from the market because of a high incidence of birth defects. It recently was approved by the FDA for the treatment of patients with leprosy and AIDS-related conditions. Recent observations that thalidomide is also an inhibitor of angiogenesis has prompted investigation into its use as an antitumor agent. Thalidomide has been shown to block angiogenesis induced by vascular endothelial growth factor. Vascular endothelial growth factor is another in the family of protein tyrosine kinase receptors and ligands. It is thought to play its role in tumorogenesis by promoting neovascularization. It has recently been shown to be up-regulated in gliomas [10]. Thalidomide has been used as single-agent therapy for malignant gliomas at recurrence and has shown modest effect. A phase II trial was conducted using thalidomide at an oral dose of 1200 mg/d for patients

with recurrent high-grade gliomas. Thirty-two patients were accrued, and 10 were evaluable for response. Of these 10 patients, 2 had a radiographic response [15]. A recent update of this data now shows a total of 4 patients with objective responses and an additional 12 patients achieving stabilization of disease lasting at least 2 months. Based on these encouraging phase II data in the setting of recurrent disease, a phase II trial has been opened in the setting of newly diagnosed patients with glioblastoma multiforme. Patients who are treated with thalidomide at the beginning of irradiation therapy continued with this therapy as long as no evidence of tumor progression is found. In addition, phase II trials are being conducted to evaluate thalidomide in combination with carboplatin or BCNU for the treatment of patients with recurrent malignant gliomas. Other angiogenesis inhibitors now being evaluated in clinical trials include platelet factor 4, interleukin-12, interferon alpha, SU5416, and TNP-470.

Chemosensitivity and anaplastic oligodendrogliomas

Oligodendrogliomas are uncommon tumors that account for only 4% to 5% of all primary brain tumors. Many oligodendrogliomas have some component of astrocytoma within them. These have been designated mixed oligoastrocytoma. Both cell types are believed to arise from a common oligodendrocyte precursor called the *oligodendrocyte type 2 astrocyte progenitor cell.*

High-grade anaplastic oligodendrogliomas and mixed anaplastic oligoastrocytomas have been found to be exceptionally chemosensitive [16]. At this time, the mechanism for chemosensitivity in oligodendrogliomas can only be speculated, and, unfortunately, a clinical or pathologic marker to distinguish patients that may have a benefit from chemotherapy has not been found.

Recently, however, molecular alterations seen in some anaplastic oligodendrogliomas have been linked to chemotherapy response and survival. Oligodendrogliomas have been found to have specific genetic alterations that distinguish them from other gliomas. The allelic loss of chromosomes 1p and 19q are a molecular signature of these tumors and occur in 50% to 70% of anaplastic oligodendrogliomas [17]. A recent study by Cairncross *et al.*[18••] showed a link between patients with anaplastic oligodendrogliomas that had loss of heterozygosity at chromosomes 1p and 19q and their response to chemotherapy.

In this study, 100% of the patients with allelic loss at chromosome 1p or combined 1p and 19q had an objective response to chemotherapy (24 of 24 and 22 of 22, respectively). In contrast, only 25% and 31% of the patients that retained these alleles had a response. The 5-year survival rate for patients with loss of heterozygosity at both 1p and 19q was 95% as opposed to a 25% 5-year survival rate in patients that retained these chromosomes.

The results of this study must still be confirmed in a larger series or by a prospective study, but these findings do suggest that a molecular marker may be used to identify chemosensitive tumors and assist in guiding treatment decisions. A phase III trial that randomizes patients with anaplastic oligodendrogliomas and mixed anaplastic oligoastrocytoma to either intensive PCV chemotherapy followed by irradiation versus irradiation alone is ongoing. As a part of the study protocol, a chromosomal analysis will also be performed. Hopefully, this study can help to answer the question of whether a survival benefit occurs with the combination of PCV and irradiation. It may also confirm the previous observation that certain molecular marker profiles may predict response.

Although some anaplastic oligodendroglioma clearly have a good response to PCV, other investigators have also reported responses in this tumor type with using BCNU, taxol,

temozolomide, VP-16, and regimens that contain platinum-based agents.

Conclusions

Unfortunately, no investigational single drug or drug combination clearly supersedes what is now considered standard therapy. Several negative studies have been published over the past year evaluating interferon [alpha] with eflornithine, taxol, MOP (*ie,* nitrogen mustard, vincristine, and procarbazine), cisplatin with ifosfamide, and others. These negative studies in the setting of recurrent malignant gliomas demonstrate the difficulty in finding effective chemotherapy for high-grade gliomas [19–21]; however, we are encouraged by the pace of research directed toward the understanding of the molecular biology of these tumors. This research will lead to the development of new drugs and combination therapies, some of which were discussed previously.

Newer attempts are also being made to modulate known mechanisms of resistance to standard drugs, such as BCNU. For instance, we know that one such mechanism of resistance involves a DNA repair protein called *alkyltransferase.* High levels of cellular alkyltransferase can repair DNA damage caused by alkylating agents. A new drug in clinical trial testing, O^6 benzylguanine, is capable of temporarily inhibiting this alkyltransferase, allowing the strategy to use O^6 benzylguanine before alkylator-based therapy. This approach has shown some promise in early trials and is being developed in the setting of recurrent malignant gliomas. Opportunities also exist to influence tumor cell growth and regulation by introduction of the *p53* gene. This gene, which is absent in many tumor cells, is important in the regulation of apoptosis [22••,23,24]. Newer gene therapy approaches include the use of an adenoviral vector capable of *p53* gene transfer into tumors deficient in this important regulator of cellular growth. All of these approaches require further testing. For chemotherapy to make a substantial improvement in survival, investigators must develop drugs that intercede earlier in the process of malignant transformation, and even then, an integrated approach with drugs that have different mechanisms of action may be required.

Finally, the discovery that some anaplastic oligodendrogliomas are uniquely chemosensitive tumors may change the future management of these patients. Conceivably, the ability to predict a durable response to chemotherapy negates the need for irradiation, thereby avoiding the long-term morbidity of this therapy. It also suggests a possibility that, in the future, patients could be stratified using specific molecular markers, thus enabling treatment and prognosis that is tailored to specific genotypic patterns of disease.

Acknowledgments

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- **Of special interest**

• • Of outstanding interest

1. Fine HA, Dear KB, Loeffler JS, Black PM, Canellos GP: Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults. Cancer 1993, 71: 2585–2597. [Context Link]

2. Levin V, Silver P, Hannigan J, Wara W, Gutin P, Davis R, Wilson C: Superiority of post-radiotherapy adjuvant chemotherapy with CCNU, procarbazine and vincristine (PCV) over BCNU for anaplastic gliomas: NCOG 6G61 final report. Int J Radiat Oncol Biol Phys 1990, 18: 321–324. [BIOSIS Previews Link] [Context Link]

3. Prados MD, Scott C, Curran W, Nelson D, Leibel S, Kramer S: PCV chemotherapy in anaplastic glioma: a retrospective review of radiation therapy oncology group (RTOG) protocols comparing survival with BCNU or PCV chemotherapy [abstract]. Neuro-oncology 1999, 1: S47. [Context Link]

4. Newlands ES, Backledge GR, Slack JA: Phase I trial of temozolomide (CCRG 81045:M&B 39831:NSC 362856). Br J Cancer 1992, 65: 287–291. [BIOSIS Previews Link] [Context Link]

5. O'Reilly SM, Newlands ES, Glaser MG: Temozolomide: a new oral cytotoxic chemotherapeutic agent with promising activity against primary brain tumors. Eur J Cancer 1993, 29A: 940–942. [BIOSIS Previews Link] [Context Link]

6.•• Freidman HS, McLendon RE, Kerby T, Dugan M, Bigner SH, Henry AJ, et al.: DNA mismatch repair and O6-alkylguanine-DNA alkyltransferase analysis and response to Temodal in newly diagnosed malignant glioma. J Clin Oncol 1998, 16: 3851–3857. The authors found that temozolomide has activity as neoadjuvant chemotherapy and AGT protein expression may identify resistant tumors. [BIOSIS Previews Link] [Context Link]

7. Levin V, Yung A, Prados M: A phase II study of Temodal in patients with anaplastic astrocytomas at first relapse [abstract]. Proc Am Soc Clin Oncol 1997, 16: 384. [Context Link]

8. Colvin O, Cokgor D, Ashley D, Kerby T, Arbuck S, Malczyn J, et al.: Irinotecan treatment of adults with recurrent or progressive malignant glioma [abstract]. Proc Am Soc Clin Oncol 1998, 17: 1493. [Context Link]

9.• Feldkamp M, Lau N, Guha A: Signal transduction pathways and there relevance in human astrocytomas. J Neurooncol 1997, 35: 223–248. A good review of signal transduction in astrocytomas. [Context Link]

10. Chan A, Leung S, Wong M, Yeun S, Cheung N, Fan Y, Chung L: Expression of vascular endothelial growth factor and its receptors in the anaplastic progression of astrocytoma, oligodendroglioma and ependymoma. Am J Surg Pathol 1998, 22: 816—826. **[Fulltext Link]** [Context Link]

11. Malkin M, Mason W, Leiberman F, Hannah A: A phase I study of SU101, a novel signal transduction inhibitor, in recurrent malignant glioma. Proc Am Soc Clin Oncol 1997, 16: 1371. [Context Link]

12.• Larner J, Jane J, Laws E, Packer R, Myers C, Shaffrey M: A phase I-II trial of lovastatin for astrocytoma and glioblastoma multiforme. Am J Clin Oncol 1998, 21: 579–583. A good discussion of farnesyltransferase inhibition. **[Fulltext Link]** [BIOSIS Previews Link] [Context Link]

13. Wojtowicz-Praga S, Dickson R, Hawkins M: Matrix metalloproteinase inhibitors. Invest New Drugs 1997, 15: 61–75. [BIOSIS Previews Link] [Context Link]

14. Brown P: Matrix metalloproteinase inhibitors in the treatment of cancer. Med Oncol 1997, 14: 1–10. [BIOSIS Previews Link] [Context Link]

15. Fine H, Loeffler J, Kyritsis A, Wen P, Black P, Levin V, et al.: A phase II trial of the anti-angiogenic agent thalidomide in patients with recurrent high-grade gliomas [abstract]. Proc Am Soc Clin Oncol 1997, 16: 1372. [Context Link]

16. Cairncross G, Macdonald D, Ludwin S, Lee D, Cascino T, Buckner J, et al.: Chemotherapy for anaplastic oligodendroglioma. J Clin Oncol 1994, 12: 2013–2021. [BIOSIS Previews Link] [Context Link]

17. Reifenberger J, Reifenberger G, Liu L, James C, Wechsler W, Collins V: Molecular genetic analysis of oligodendroglial tumors shows preferential allelic deletions on 19g and 1p. Am J Pathol 1994, 145: 1175–1190. [BIOSIS Previews Link] [Context Link]

18.•• Cairncross G, Ueki K, Zlatescu M, Lisle D, Finkelstein D, Hammond R, et al.: Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. J Natl Cancer Inst 1998, 90: 1473–1479. The authors found allelic loss of chromosomes 1p and 19q was associated with chemosensitivity and survival in patients with anaplastic oligodendrogliomas. [BIOSIS Previews Link] [Context Link]

19. Buckner J, Burch P, Cascino T, O'Fallon J, Scheithauer B: Phase II trial of recombinant interferon alpha 2a and eflornithine in patients with recurrent glioma. J Neurooncol 1998, 36: 65–70. [Context Link]

20. Galinis E, Buckner J, Burch P, Schaefer P, Dinapoli R, Novotny P, et al.: Phase II trial of nitrogen mustard, vincristine and procarbazine in patients with recurrent glioma: North Central Cancer Treatment Group results. J Clin Oncol 1998, 16: 2953–2958. [BIOSIS Previews Link] [Context Link]

21. van den Bent M, Schellens J, Vecht C, Smit P, Loosveld O, Ma J, et al.: Phase II study on cisplatin and ifosfamide in recurrent high grade gliomas. Eur J Cancer 1998, 34: 1570–1574. [BIOSIS Previews Link] [Context Link]

22.•• Freidman H, Kokkinakis D, Pluda J, Freidman A, Cokgor I, Haglund M, et al.: Phase I trial of O6 Benzylguanine for patients undergoing surgery for malignant glioma. J Clin Oncol 1998, 16: 3570–1375. The results suggest a dose of O6-BG that should inhibit the DNA repair enzyme AGT for 18 hours. [BIOSIS Previews Link] [Context Link]

23. Jaeckle K, Eyre H, Townsend J, Schulman S, Knudson H, Belanich M, et al.: Correlation of tumor O6 methylguanine-DNA methyltransferase levels with survival of malignant astrocytoma patients treated with bis-chloroethylnitrosourea: a Southwest Oncology Group study. J Clin Oncol 1998, 16: 3310–3315. [BIOSIS Previews Link] [Context Link]

24. Trepel M, Groscurth P, Malipiero U, Gulbins E, Dichgans J, Weller M: Chemosensitivity of human malignant glioma: modulation by p53 gene transfer. J Neurooncol 1998, 39: 19–32. [Context Link]

Section Description

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Novel chemotherapeutic agents for the treatment of brain cancer

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Abstract

Brain cancer encompasses both primary and metastatic brain tumours and accounts for over 120,000 new patients each year. Despite aggressive therapy, the majority of patients with brain cancer have poor prognosis and have brief survival intervals. Current chemotherapy drugs, used alone or in combination, have minimal or only modest activity. Novel agents that have recently been applied to brain cancer include temozolomide, irinotecan and paclitaxel. Temozolomide is a DNA alkylating agent, irinotecan inhibits DNA topoisomerase I and paclitaxel binds to microtubules and induces polymerisation. Neoplastic angiogenesis and brain tumour invasion are also targets for therapeutic intervention with new agents such as thalidomide, suramin and marimastat. All of these agents have demonstrated activity against brain cancer in vitro. Several of the drugs, in particular temozolomide, paclitaxel and irinotecan, have entered preliminary clinical trials and have demonstrated some efficacy. However, chemotherapy for primary brain tumours remains rather non-specific and mostly ineffective. The use of chemotherapy may be more effective against selected metastatic brain tumours. Continued basic research is needed to further elucidate the genetic basis of transformation, tumour invasion and angiogenesis. It is hoped that this research will lead to new therapeutic targets for drug design and development. In addition, new strategies must be developed to overcome the problem of chemotherapy resistance